

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
22 January 2004 (22.01.2004)

PCT

(10) International Publication Number  
**WO 2004/006961 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 47/36**,  
47/38, A61L 27/20, 27/38, A61P 19/02

5-4219, Beaubien Street East, Montréal, Québec H1T 1S5  
(CA).

(21) International Application Number:  
PCT/CA2003/001069

(74) Agent: OGILVY RENAULT; Suite 1600, 1981 McGill College Avenue, Montreal, Québec H3A 2Y3 (CA).

(22) International Filing Date: 16 July 2003 (16.07.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English  
(26) Publication Language: English  
(30) Priority Data:  
60/395,991 16 July 2002 (16.07.2002) US

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **BIO SYNTech CANADA INC. [CA/CA]**; 475 Armand-Frappier Blvd., Laval, Québec H7V 4B3 (CA).  
(72) Inventors; and  
(75) Inventors/Applicants (*for US only*): **CHENITE, Abdellatif** [CA/CA]; 28 Bethune, Kirkland, Québec H9H 4H6 (CA). **HOEMANN, Caroline** [CA/CA]; 4329 King Edward, Montréal, Québec H4B 2H4 (CA). **BUSCHMANN, Michael** [CA/CA]; 4329 King Edward, Montréal, Québec H4B 2H4 (CA). **SEREQI, Alessio** [CA/CA]; 840 Dollard, Montréal, Québec H2V 3G7 (CA). **SUN, Jun** [CA/CA];

**Published:**

— *with international search report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**WO 2004/006961 A1**

(54) Title: COMPOSITION FOR CYTOKOMPATIBLE, INJECTABLE, SELF-GELLING CHITOSAN SOLUTIONS FOR ENCAPSULATING AND DELIVERING LIVE CELLS OR BIOLOGICALLY ACTIVE FACTORS

(57) **Abstract:** The present invention provides compositions and methods for tissue repair using a cytocompatible self-gelling cross-linked hydrogel. The composition comprises a biocompatible mixture of chitosan, bifunctional dialdehyde, and hydroxylated polymer, which can be used to immobilize or encapsulate viable cells, or bioactive substances. The method includes the process of mixing bioactive substances, live cells, and/or extracellular matrix components with a cross-linking solution comprising a bifunctional aldehyde-treated hydroxylated polymer such as hydroxyethyl cellulose. The cross-linking solution is then mixed homogenously with a neutral isotonic chitosan solution. The chitosan becomes cross-linked by the bifunctional aldehyde, while the cells are protected from potentially nocive effects of the aldehyde cross-linker by the hydroxylated polymer. The injectable solution retains cell viability and bioactivity, and immobilizes cells at the site of injection or delivery. Depending on the particular application, mixtures of chitosan and bifunctional dialdehyde may be employed. The injectable solution also liberates bioactive substances with controlled release kinetics from the site of injection.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/03/01069

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K47/36 A61K47/38 A61L27/20 A61L27/38 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, COMPENDEX

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 03 042250 A (BIOSYNTECH CANADA INC ;DABBARH FOUAD (CA); SELMANI AMINE (CA); CHA) 22 May 2003 (2003-05-22)  page 7, paragraph 1 -page 9, paragraph 2; claims 1,10,16-19 ---	1-3, 9-15, 18-20, 30-44
X	US 5 489 401 A (FREEMAN AMIHAY) 6 February 1996 (1996-02-06) cited in the application column 3, line 5 - line 59 --- -/-	1-3, 9-16, 18-29

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the International search

21 October 2003

Date of mailing of the International search report

05/11/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Bochelen, D

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/03/01069

## C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 895 724 A (CARDINAL JOHN R ET AL) 23 January 1990 (1990-01-23)	1-3, 9-14, 20-30, 32,37, 41,43
Y	column 4, line 58 -column 5, line 7 column 5, line 8 - line 22 ---	4-8
Y	WO 99 47186 A (SUH JUN KYO ;FU FREDDIE H (US); MATTHEW HOWARD (US); UNIV PITTSBUR) 23 September 1999 (1999-09-23) claims 8,17,18,31 ---	31-36, 38-43
Y	FRANCIS SUH J-K ET AL: "Application of chitosan-based polysaccharide biomaterials in cartilage tissue engineering: a review" BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 21, no. 24, 15 December 2000 (2000-12-15), pages 2589-2598, XP004217422 ISSN: 0142-9612 page 2591, column 2 -page 2594, column 1 ---	31-36, 38-43
Y	SUTO SHINICHI ET AL: "Chemical crosslinking of hydroxypropyl cellulose and chitosan blends" J APPL POLYM SCI;JOURNAL OF APPLIED POLYMER SCIENCE SEP 26 1996 JOHN WILEY & SONS INC, NEW YORK, NY, USA, vol. 61, no. 13, 26 September 1996 (1996-09-26), pages 2273-2278, XP002258373 page 2274, column 1 ---	4-8
A	RUEL-GARIEPY E ET AL: "CHARACTERIZATION OF THERMOSENSITIVE CHITOSAN GELS FOR THE SUSTAINEDDELIVERY OF DRUGS" INTERNATIONAL JOURNAL OF PHARMACEUTICS, AMSTERDAM, NL, vol. 203, 10 August 2000 (2000-08-10), pages 89-98, XP000997714 ISSN: 0378-5173 the whole document -----	1-44

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 03/01069

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 31-35 and 41-43 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple Inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/CN03/01069

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 03042250	A	22-05-2003	WO US	03042250 A1 2003129730 A1		22-05-2003 10-07-2003
US 5489401	A	06-02-1996	IL CA EP JP	100096 A 2082352 A1 0543572 A1 7222922 A		31-03-1996 21-05-1993 26-05-1993 22-08-1995
US 4895724	A	23-01-1990		NONE		
WO 9947186	A	23-09-1999	AU WO	3097999 A 9947186 A1		11-10-1999 23-09-1999